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## THE DIAGNOSTIC VALUE OF INTRACUTANEOUS INJECTION OF DIPHTHERIA TOXIN (SCHICK REACTION)\*

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By means of the Schick intracutaneous reaction, individual susceptibility and immunity to diphtheria may be readily recognized with a fair degree of accuracy. This has been turned to account in the selection of persons requiring immunization in the presence of exposure to diphtheria and in the sparing of those, already protected, from further annoyance and discomfort and from needless sensitization to horse serum. This reaction has also facilitated the study of the immunizing effects of injections of diphtheria toxin-antitoxin mixtures, as advocated by Behring. Schick has also employed the reaction to determine the quantity of diphtheria antitoxin required to bring a person infected with diphtheria into the condition of an immune individual and so to determine the doses of antitoxin required in various sorts of cases. It has also been valuable in estimating the relative efficiency of single and multiple injections of antitoxin and of injections made in various ways.

The technic of the test as devised by Schick<sup>1</sup> and followed by others is simple and readily applied. First, the minimum fatal dose (M. L. D.) of the diphtheria toxin is determined for a guinea-pig of 250 gm. The toxin is then so diluted that each cubic centimeter contains 0.2 of the M. L. D. Of this dilution, 0.1 c.c. (0.02 M. L. D.) is injected into the skin. The injection is made with a very fine, sharp, short-pointed needle, and a successful injection results in the production of a white, blister-like, punctate-appearing elevation. The traumatic disturbance disappears in a few hours, and if there is antitoxin in the blood of the injected person no further changes occur. This is regarded as a negative result and indicates that the person is immune to infection by diphtheria bacilli. If the person has very little or no diphtheria antitoxin in the blood, the disappearance of the traumatic

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1. München. med. Wchnschr., 1913, 60, p. 2608.

disturbance is followed by a gradually increasing redness and infiltration at the site of injection. This reaches its height in twenty-four to forty-eight hours, persists several days, and gradually fades leaving a brownish pigmentation and slight desquamation. This is designated a positive reaction. Sometimes individuals who have antitoxin in the blood show some local redness and infiltration. This is not due to the toxin injected since it may follow the injection of the same amount of toxin combined with many times the amount of antitoxin necessary to neutralize it. These so-called false reactions usually come on more rapidly than the true ones, the redness is less sharply outlined, the local infiltration is more marked, and they disappear in two to four days with no subsequent desquamation and little or no pigmentation.

During the later part of the year 1914 in the Durand Hospital, we have given the intracutaneous toxin injection in all cases of diphtheria and suspected diphtheria at the time of admission, and we have employed it in all incoming interns and nurses. The technic has been that indicated. The injections have been made into the skin of the outer side of the middle third of the arm. Those reactions have been considered positive in which a redness and some induration appeared after twenty-four hours and persisted for six to ten days with succeeding pigmentation and scaling. Whenever slight redness appeared inside of twenty-four hours and rapidly subsided with no later pigmentation and scaling it was considered a false reaction. Some individuals, who were immune to diphtheria, exhibited marked redness in twenty-four hours which quickly subsided leaving no further signs. In cases giving a false reaction, we have found that a control injection in the opposite arm of the same amount of toxin combined with 1,000 times the amount of antitoxin required for neutralization, as advised by Groër and Kassowitz,<sup>2</sup> sometimes also calls forth a false reaction. Groër and Kassowitz conclude from a large experience that a negative result from the toxin injection in adults signifies that there is antitoxin in the blood, but that a positive result does not indicate an absence of antitoxin except when the reaction with the toxin-antitoxin mixture is negative. They found that a considerable number (47.5 per cent) of mothers of new-born children react positively from the intracutaneous injection of diphtheria toxin in spite of the presence of normal antitoxin in the blood. In these individuals, toxin neutralized by antitoxin in vitro also causes positive reactions. They designate

2. Ztschr. f. Immunitätsf. u. exper. Therap., 1914, 23, p. 108.

such reactions "paradoxical." Similar reactions with the toxin-antitoxin mixture occurred in mothers with no antitoxin in the blood, so that 56 percent of mothers give paradoxical reactions. They found that 11.2 percent of new-born infants are insusceptible to specific diphtheria toxin inflammation even in a poverty of antibodies, so that a negative result with the intracutaneous test in these cases must not be considered final. In a number of the women they obtained no reaction by injections of dilute solutions of broth and horse serum, or of pure antidiphtheritic serum. To explain these paradoxical reactions they have advanced certain theories. One group of theories rests upon the assumption that the individual for some reasons is unable to neutralize diphtheria toxin within the body; the other class of theories attempts to explain the reaction as one of allergy.

Many of our tests have been controlled by estimates of the antitoxin in the blood of the injected individuals, employing Römer's method. No estimates were made for less than 0.04 unit of antitoxin per cubic centimeter of blood. That this method measured the antitoxin accurately was shown by controlling the results by tests made according to the usual method for testing the potency of antidiphtheritic serum.

Of ten normal young adults, interns and nurses, six gave negative and four positive reactions. In each of these ten individuals the blood serum was tested for its antitoxin content. In each of the four who reacted positively the antitoxin was less than 0.04 unit per cubic centimeter of blood. Of the six cases giving negative reactions, one had 0.04 unit, two had 0.125 unit, and three had 2 units per cubic centimeter of blood. The proportion of those giving positive Schick reactions is rather high, but the number of observations is relatively small for comparison. Park, Zingher, and Serota<sup>3</sup> in one hundred and twenty-four persons of 15 years and over obtained positive results in thirty-one, or 25 percent.

Schick<sup>1</sup> has collected two hundred and sixty-four observations in persons from 5 to 15 years of age, 50 percent of whom gave positive reactions. In adults, the proportion of positive reactions was still smaller. The proportions of positive reactions occurring at various ages, as determined by Schick and by Park, Zingher, and Serota, correspond very closely. From the second to the fifth year positive reactions occurred in about 65 percent of the cases observed. Groër

3. Arch. Pediat., 1914, 31, p. 481.

and Kassowitz<sup>2</sup> found that 84 percent of new-born children and their mothers have a considerable amount of normal diphtheria antitoxin in the blood serum. Two of the nurses in our series who gave negative results had received diphtheria antitoxin for diphtheria two and four years before, respectively. Nurses giving positive reactions are immunized with diphtheria antitoxin at intervals during their stay in the hospital.

The test was applied in fourteen cases of angina which proved not to be diphtheria. Twelve of these cases were tonsillitis, ten of which reacted negatively and two positively. In two of these cases giving negative reactions, diphtheria bacilli were present in throat cultures. In one of them the blood serum contained 0.04 unit and in the other 5 units of antitoxin per cubic centimeter. In four cases giving negative reactions, the simultaneous injection of antitoxin may have influenced the result. In a case of Vincent's angina, the reaction was negative, the blood serum containing 0.04 unit of antitoxin per cubic centimeter. In a case of secondary syphilis with a positive Wassermann, the Schick test resulted negatively and the blood serum contained fifteen units of antitoxin per cubic centimeter. The value of the test as a diagnostic aid in cases of angina of uncertain character is apparent. It often enables a differentiation to be made between diphtheria and tonsillitis and other infections in which the patient is a diphtheria bacillus carrier. The latter cases could hardly be benefitted by diphtheria antitoxin. Park and Zingher<sup>4</sup> have found the Schick test of value as a diagnostic measure in cases with a purulent or sanious nasal discharge showing the diphtheria bacillus, in which it is difficult to decide whether the case is a carrier or a beginning diphtheria. A negative result excludes diphtheria. Reiche<sup>5</sup> has reported twenty-three cases which clinically and bacteriologically were Vincent's angina, but in which diphtheria bacilli were also found in the throat. Some of these he believed to have been diphtheria bacillus carriers. The diagnostic value of the Schick test in such cases is very evident.

Four cases admitted as diphtheria bacillus carriers were tested and all gave negative results. In three there was a history of slight sore throat some time before admission. In one case the antitoxic content of the blood was six units per cubic centimeter, in another it was fifteen units per cubic centimeter. In a third case the antitoxin in the blood

4. Proc. New York Path. Soc., 1914, 14, p. 151.

5. Med. Klin., 1914, 10, p. 1345.

increased from five to ten units per cubic centimeter during the first week in the hospital. The fourth case came to the hospital just about the time of the recovery of the sore throat. At this time there was less than 0.04 unit of antitoxin per cubic centimeter of blood. In the two following weeks it rose to thirty units per cubic centimeter. These observations seem to indicate a pronounced production of antitoxin in mild cases of diphtheria which recover spontaneously. Other observers have found that diphtheria bacillus carriers have relatively abundant antitoxin in the blood. These facts speak in favor of the theory advanced by German writers which ascribes the frequent presence of normal antitoxin in the blood to a former, slight infection by diphtheria bacilli, often so mild as to have failed to attract attention. Park and Zingher<sup>4</sup> have pointed out that the normal antitoxin may be due to other factors, as they often found all the children of a family to react similarly, giving either positive or negative results. In these instances the influences of former mild family infections would be excluded with difficulty.

Groër and Kassowitz<sup>6</sup> have thoroughly studied the normal diphtheria immunity in man and concluded that the antidiphtheritic substance found in normal serum is identical in physical and chemical properties with immune antitoxin.

In ten cases of acute diphtheria we tested the blood serum for antitoxin at the time of admission before any antitoxin had been administered. In every instance it was below 0.04 unit per cubic centimeter. This agrees with the conclusions of all observers that an absence of normal antitoxin is essential for infection by diphtheria bacilli. The amount of antitoxin required for protection is usually stated to be 0.03 + unit per cubic centimeter of blood, but Behring believes that 0.01 unit per cubic centimeter is sufficient. Park, Zingher, and Serota<sup>3</sup> injected a child, weighing 35 pounds, with 10 units of antitoxin and twenty-four hours later the Schick reaction was prevented. The antitoxin in the blood could scarcely have been more than 0.01 unit per cubic centimeter. In twelve cases of diphtheria the toxin injection was given on admission and antitoxin was injected immediately afterward. Four cases received 5,000 units each, two reacting positively and two negatively; one received 6,000 units and reacted negatively; three received 10,000 units each, two reacted positively and one negatively; four received 20,000 each, two reacted

6. *Ztschr. f. Immunitätsf. u. exper. Therap.*, 1914, 22, p. 404.

positively and two negatively. Thus, it appears that the reaction is prevented or modified by sufficient antitoxin given simultaneously. In some of the reactions recorded as negative there was a very slight, modified, or abortive reaction. In all cases of diphtheria tested after the disease had been controlled by antitoxin, the cutaneous reaction was negative.

#### CONCLUSIONS

In normal persons a negative result from the intracutaneous injection of diphtheria toxin constantly indicates the presence in the blood of diphtheria antitoxin with a consequent immunity to diphtheria, at least for the time being. A typical positive result points to an absence of antitoxin and a resulting susceptibility to infection by diphtheria.

In the presence of exposure to diphtheria, immunization by injections of antitoxin is not indicated in persons who give negative reactions, but only in those who give positive reactions.

Intracutaneous injections of diphtheria toxin are valuable in separating cases of infection by diphtheria bacilli from cases of angina and rhinitis due to other causes. They also serve to distinguish cases which are diphtheria from those which are only bacillus carriers.

Diphtheria bacillus carriers usually develop relatively large amounts of antitoxin in the blood.

In the acute stage of diphtheria, before any antitoxin has been injected, the patient's blood contains little or no antitoxin.

In cases of acute diphtheria, full doses of antitoxin given simultaneously with the toxin injection frequently modify or completely inhibit the cutaneous reaction.